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BRIEF REPORT

Chronic myeloid leukemia following treatment for bilateral retinoblastoma

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CML	Chronic myeloid leukemia
RB	Retinoblastoma

ABSTRACT

In contrast to their higher incidence of radiation-induced solid tumors, patients with bilateral retinoblastoma (RB) have a low risk of developing therapy-related hematological malignancies. We present the first case of a patient with bilateral RB to develop chronic myeloid leukemia (CML) 15 years after multimodality therapy, comprising systemic chemotherapy and external beam radiation to the orbits. We discuss the possible etiology of therapy-related CML in long-term survivors with bilateral RB, although the possibility of *de novo* CML cannot be completely excluded in the present case.

INTRODUCTION

The overall survival rate of patients with intraocular retinoblastoma (RB) exceeds 95%.[1] In addition to conventional treatment modalities, such as enucleation and external beam radiation, systemic chemotherapy, focal laser therapy, cryotherapy, brachytherapy, and the recently established selective ophthalmic arterial and intravitreal injection have been performed for ocular salvage and vision preservation.[2–4] Since the majority of patients with RB now survive into adulthood, late adverse effects have become a focus for clinical and research areas. Therapy-related malignancy is one of the most severe late adverse effects.[1] Patients with bilateral RB, who invariably have germline *RB* gene mutation, are at significant risk of therapy-related malignancy.[5] In contrast to their higher incidence of radiation-induced solid tumors, patients with bilateral RB have a low risk of developing therapy-related hematological malignancies,[5–8] and the etiologies of therapy-related hematological malignancies in these patients remain largely unknown.

In the present study, we report a rare case who developed chronic myeloid leukemia (CML) 15 years after the treatment for bilateral RB.

RESULTS

A 4-month-old male infant with bilateral RB was successfully treated by enucleation of the right eye, 41.8 Gy of external beam radiation to the orbits, 6 months of chemotherapy with vincristine and cyclophosphamide, and cryotherapy and photocoagulation for the left eye. He had no family history of malignancy. He experienced local relapse with vitreous seeding four times thereafter, during

which he received multiple rounds of systemic chemotherapy, comprising etoposide, cyclophosphamide, and pirarubicin, in combination with intra-arterial and intravitreal injections of melphalan, cryotherapy, and brachytherapy for the left eye. He finally underwent enucleation of the left eye at the age of 10 years, which resulted in long-term remission. The cumulative doses of chemotherapy drugs were as follows: etoposide, 1000 mg/m^2; cyclophosphamide, 19.6 g/m^2; pirarubicin, 310 mg/m^2; cisplatin, 90 mg/m^2; carboplatin, 750 mg/m^2; and vincristine, 51 mg/m^2.

At 25 years old, laboratory studies during annual follow-up revealed a white blood count count of 32.3 ×10^9/L (myelocytes, 11%; metamyelocytes, 2%; neutrophils, 69%; basophils, 5%; monocytes, 4%; lymphocytes, 9%), hemoglobin of 14.0 g/dL, and a platelet count of 218 ×10^9/L, although he did not have any clinical symptoms. Biochemical examination revealed marked elevation of lactate dehydrogenase (711 U/L) and uric acid (7.3 mg/dL). Bone marrow aspiration revealed distinct hypercellularity and a markedly increased myeloid:erythroid ratio (8.43) without increased blasts. Karyotype analysis demonstrated a chromosome translocation, 46, XY, t(9;22)(q34;q11.2), in all 20 bone marrow cells analyzed. Detection of the major *BCR-ABL* fusion gene transcripts (2.9 × 10^6 copies/μgRNA) on quantitative polymerase chain reaction led to a diagnosis of CML in chronic phase. Treatment with dasatinib (100 mg/day) normalized the white blood count within 1 month. Bone marrow aspiration after 3 months revealed normocellular marrow, and the quantitative polymerase chain reaction revealed a 4.2 log reduction of the major *BCR-ABL* fusion gene transcripts (1.7 × 10^2 copies/μgRNA). Fluorescence *in situ* hybridization analysis for the *BCR-ABL* fusion gene and cytogenetic karyotyping results were normal, achieving complete

cytogenetic response and an optimal response, according to the European LeukemiaNet recommendations.[9]

DISCUSSION

Patients with bilateral RB have a high risk of developing secondary malignancies, with a cumulative incidence of approximately 30% at 40–50 years from diagnosis.[6, 8] About half of secondary malignancies are bone and soft tissue sarcomas, while only 0.5–0.6% are hematological malignancies (Table 1).[6–8] Although various types of leukemia and lymphoma have been observed as secondary hematological malignances in patients treated for RB, there are no reports of secondary CML. Moreover, etoposide or alkylator-containig chemotherapy, does not increase the risk of secondary CML in the general population.[10] Overall, there is no clear reason to assume an association between chemotherapy and development of CML in the present case.

Howard et al. identified 164 patients with secondary CML in 376,835 long-term survivors with breast cancer, representing an excess absolute risk of 2.06 per 100,000 person-years.[11] Dose-dependent increased risk of radiation-related CML has also been demonstrated in patients with cervical cancer and ankylosing spondylitis, and in Japanese atomic bomb survivors.[12] The frequency of secondary CML has decreased over time, possibly due to the recent progress in radiation therapy techniques that allow minimal exposure of the bone marrow to radiation.[11] Secondary CML is an extremely rare event in patients with RB, considering that approximately 80% of patients received radiation therapy,[6, 8] which might be explained by the limited field of

93 radiation to the periorbital bone marrow. Thus, CML in the present case is likely associated with

94 radiation therapy, although the possibility of *de novo* CML cannot be completely excluded.

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96 **CONFLICT OF INTEREST**

97 The authors declare no conflict of interest associated with this manuscript.

REFERENCES

1. Dimaras H, Kimani K, Dimba EA et al. Retinoblastoma. *Lancet.* 2012;379:1436-1446.
2. Suzuki S, Yamane T, Mohri M, et al. Selective ophthalmic arterial injecsion therapy for intraocular retinoblastoma: the long-term prognosis. *Opthalmology.* 2011;118:2081-2087.
3. Schueler AO, Flühs D, Anastassiou G, et al. Beta-ray brachytherapy with 106Ru plaques for retinoblastoma. *Int J Radiat Oncol Biol Phys.* 2006;65:1212-1221.
4. Kaneko A, Suzuki S. Eye-preservation treatment of retinoblastoma with vitreous seeding. *Jpn J Clin Oncol*. 2003;33:601-607.
5. Kleinerman RA, Yu CL, Little MP, et al. Variation of second cancer risk by family history of retinoblastoma among long-term survivors. *J Clin Oncol.* 2012;30:950-957.
6. Kleinerman RA, Tucker MA, Tarone RE, et al. Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: an extended follow-up. *J Clin Oncol.* 2005;23:2272-2279.
7. MacCarthy A, Bayne AM, Brownbill PA, et al. Second and subsequent tumours among 1927 retinoblastoma patients diagnosed in Britain 1951-2004. *Br J Cancer.* 2013;108:2455-2463.
8. Marees T, Moll AC, Imhof SM, et al. Risk of second malignancies in survivors of retinoblastoma: more than 40 years of follow-up. *J Natl Cancer Inst.* 2008;100:1771-1779.
9. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood.* 2013;122:872-884.
10. Lichtman MA. Is there an entity of chemically induced BCR-ABL-positive chronic

myelogenous leukemia? *Oncologist.* 2008;13:645-654.

11. Howard RA, Gilbert ES, Chen BE, et al. Leukemia following breast cancer: an international population-based study of 376,825 women. *Breast Cancer Res Treat.* 2007;105:359-368.

12. Little MP, Weiss HA, Boice JD Jr, et al. Risks of leukemia in Japanese atomic bomb survivors, in women treated for cervical cancer, and in patients treated for ankylosing spondylitis. *Radiat Res.* 1999;152:280-292.